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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,897	12/29/2003	Anthony Joonkyoo Yun	PALO-002	7432

24353 7590 09/21/2011

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
09/21/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,897	YUN ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *85-109* is/are pending in the application.

5a) Of the above claim(s) *89,90,105 and 106* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *85-88,91-104 and 107-109* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/20/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/12/2010 has been entered.

Applicants' in the response to restriction/election dated 3/12/2007 elected (species) propranolol as beta blocker, NSAID as non-beta blocker and aging associated condition and loss of parasympathetic function as sub species. Applicants' have cancelled claims 1-84 and have added new claims 85-109. Claims 89, 90, 105, 106 do not read on the elected species. Claims 85-88, 91-104, 107-109 are being examined on the merits herein.

Response to Arguments/Remarks

Applicants' cancellation of all claims and addition of new claims necessitated the new rejections presented in this action. Applicants' arguments regarding the rejections have been fully considered but are moot in view of the new rejections presented in this office action. Accordingly the action is made non final.

Application Priority

This application filed 12/29/2003 claims Priority from Provisional Application 60510008, filed 10/08/2003.

Information Disclosure Statement

The information disclosure statement (IDS) filed on 8/20/2010 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the IDS is being considered by the Examiner.

Specification

The specification is objected to because of the following informalities: Page 1, para [0001], line 2 is missing the provisional application number for claims priority. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 85-88, 91-104, 107-109 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims are directed to a method comprising providing a subject known to suffer from an aging associated condition; determining the state of the autonomic nervous system by measuring a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system; evaluating the parasympathetic activity/sympathetic activity ratio to determine if modulation of the autonomic nervous system is needed; and administering to said subject an effective amount of at least one beta- blocker if modulation of the autonomic nervous system is needed to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's

autonomic nervous system that is analogous to the parasympathetic activity/ sympathetic activity ratio observed in a healthy 25 year old human subject to treat said subject for said aging associated condition.

The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. The specification in general teaches the dosage administration, routes, types of delivery, a list of beta blockers and non-beta blockers. The specification does not teach administration of a beta-blocker along with a non-beta blocker to a subject known to suffer from any of the aging associated condition. Applicants in the specification teaches that aging associated conditions include atherosclerotic disease, cancer, osteoporosis, viral infections, allergic conditions, and sepsis (para 0205), Stroke, heart diseases, arthritis, depression, Alzheimer's, Parkinson's, age related vision disorders such as macular degeneration, cataract, diabetic retinopathy, glaucoma. This list is not comprehensive as it may include other conditions like tumors, kidney diseases, incontinence, other neurodegenerative conditions and so forth. The specification does not provide data or show any examples of actual administration of beta blockers along with a non-beta blocking agent in any of the conditions claimed. The scope of the aging associated conditions is very large. Cancer is in itself encompasses different types of cancers and there has never been a compound capable of treating all types of cancers. There are compounds that treat a range of cancers, but no one has ever been able to figure out

how to get a compound to treat cancers generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective anti-tumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. It cannot be predicted from the prior art or from the specification that administration of a beta blocker (at any concentration) and modulating the autonomic nervous system to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/ sympathetic activity ratio observed in a healthy 25 year old human subject to treat said subject for said aging associated condition such as cancer in general. The scope of the aging associated conditions, beta blockers, non-beta blockers and the concentrations of such compounds are very large. It would be an undue experimentation of a person of ordinary skill in the art at the time of the invention to find which beta blocker is useful and the effective concentration of the same to modulate the autonomic nervous system to treat the specific aging associate condition. The specification does not give any specific guidance to treating of age associated conditions regarding (1) criteria for the dosages for specific age associated conditions (2) criteria for the counter indications in giving such beta

blockers (3) criteria of dosage regimens for specific conditions e.g. when the dose needs to be administered, how many doses etc. (4) criteria if patients suffer from multiple associated conditions. For example, propranolol document (http://www.drugs.com/pro/propranolol.html) lists the contraindications, adverse effects, drug interactions with other drugs etc. A person of skilled in the art have to consider such factors before administering a drug to a patient, also in combination therapy especially in older patients. This is just for one beta blocker which has been well studied as the drug was approved by FDA in 1967. The older patients can have multiple disease conditions and the therapy has to be patient specific and the conditions need to be monitored and it is not a trivial matter. Accordingly, the scope of the claims is broad. Also, the method claims comprise administering at least one non-beta blocker (claims 85 and 96) in addition to administration of at least one beta-blocker. A non-beta blocker can be any agent other than beta blockers. In a nutshell the claim is towards administration of any number of beta blockers with any number of non-beta blockers or all the drugs that are available. Accordingly, the scope is extensive and potentially involves undue experimentation. The specification has not given any guidance (1) in regards with counter indications of all the non-beta blockers claimed (2) the dosage amount to be provided with respect to age related conditions to make sure there are no adverse effects or the side effects are to a minimal (3) precautions in administration of drugs for patients with more than one condition. The specification does not provide adequate description and there are no specific examples to provide support to the claims. The claim(s) contains subject matter, which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not provide support to the subject matter of administration of a beta blocker and a non-beta blocking agent to a subject to treat the said subject for at least one of the aging associated conditions as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and, (8) the quantity of experimentation necessary.

Claims 85-88, 91-104, 107-109 are rejected under 35 U.S.C. 112, first paragraph, because the prior art, while being enabling for a method of treating a subject for an aging associated condition comprising administering an effective amount of at least one beta blocker to conditions like hypertension, glaucoma, migraine, anxiety disorders does not reasonably provide enablement for all the aging associated conditions with all the beta blockers and in combination with all non-beta blocking agents as claimed in 85 and 96. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

(1, 5) The nature of the invention and the breadth of the claims:

The instant claims are directed to a directed to a method comprising providing a subject known to suffer from an aging associated condition; determining the state of the autonomic nervous system by measuring a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system; evaluating the parasympathetic activity/sympathetic activity ratio to determine if modulation of the autonomic nervous system is needed; and administering to said subject an effective amount of at least one beta- blocker if modulation of the autonomic nervous system is needed to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/ sympathetic activity ratio observed in a healthy 25 year old human subject to treat said subject for said aging associated condition. The claims are not limited to any dosage amounts. Claims 95, 98, 99 are limited to beta blocker propranolol. The claims 85-88, 91-94, 96, 97, 100-104, 107-109 are very broad with respect to the conditions, number of beta blockers, to the dosage amounts and to a number of non-beta blocking agents.

(3) The relative skill of those in the art:

The relative skill of those in the pharmaceutical and medical arts is high, requiring advanced education and training.

(2) The state of the prior art:

Stockley (Are Beta blockers safe?, BMJ, 298, 10 Jun 1989) teaches that two patients developed cardiac failure upon administration of nifedipine (a non-beta blocker listed in the specification, para 0076) along with propranolol or atelenol or alprenolol (p 1584, para 2). Chester et al. (Chest 79, 5, May 1981) teaches adverse effects of propranolol on airway function in nonasthmatic chronic obstructive lung disease patients (see Abstract). Houston (Cardiol Clin, 1986, Feb 4(1), 117-35) teaches that several antihypertensive drugs have an adverse effect on glucose tolerance that may partially or completely negate the beneficial effects of reducing blood pressure as it relates to the incidence of coronary heart disease and its complications and beta-blockers without intrinsic sympathomimetic activity have the greatest adverse effect on glucose intolerance. Liebermann et al. (Br J Obstet Gynaecol, 1978, 678-83, abstract) teaches that beta-adrenergic blockade is harmful to the hypoxic fetus, for these reasons the use of propranolol in hypertensive pregnancies complicated by placental insufficiency may be contraindicated unless there is no satisfactory alternative (See Abstract). Allen et al. teaches that there was an adverse effect of practolol, the occurrence of sinus bradycardia with or without an increase in the frequency of ventricular ectopic beats (See abstract). It has been well known in the prior art that beta blockers are useful in the treatment of angina, heart failure, high blood pressure, glaucoma and various disorders (http://en.wikipedia.org/ wiki/Beta_blocker). Salpeter et al. (Cochrane Database of Systemic Reviews, 4, 2002) teach that beta blocker therapy has mortality benefits in patients with hypertension, heart failure, coronary artery disease as well as during the postoperative period (see Abstract). Also drugs that modulate adrenergic receptors

such as beta blockers (e.g., metoprolol, atenolol) are known to cause inflammation to the joint (See Savola, BMJ, 287, 1983). In summary, the guidance from prior art is for the use of beta blockers in conditions like hypertension, heart failure, coronary artery disease as well as during the postoperative period, glaucoma etc., the adverse effects of certain beta blockers and the contraindications of beta blockers in combination with calcium channel blockers. The prior art or the specification does not teach that every single disease or disorder in the different classes of disorders (that are etiologically different) and are associated with aging will be effectively treated by administration of the beta blockers (known and yet to be discovered) nor does the prior art or specification teach that every combination of beta blocker with a non-beta blocking agent can be used without interactions and be effective in the treatment.

(4) The predictability of the art:

Despite the advance training of those in the art, the art is highly unpredictable. It is still not possible to predict the pharmacological activity or treatment efficacy of a compound based on the structure alone. It is also not possible to predict the efficacy of a given class of compounds for the treatment of a particular disease absent a mechanistic link between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Typically, in order to verify that a compound will be effective in treating a disease, the compounds must be either tested directly in a patient or in a model that has been established as being predictive of treatment efficacy. In order to predict whether a class of compounds would be effective in treating a disease, the etiology or pathophysiology of the disease must be uncovered, and there

should be a nexus between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Absent experimental tests verifying the efficacy of a compound or a strong nexus between the known pharmacological activity of a class of agents and the etiology and/or pathophysiology of the condition, it is impossible to predict whether the compound or class of compounds (here beta blockers) would actually be effective for treating every single aging associated condition. It is impossible to predict that every single beta blocker can be used in combination with every single non-beta blocker class of compounds to treat an aging associated condition like cancer. It is impossible to predict that every single beta blocker at all concentrations will be useful in treating all types of cancer or tumors and treat neurodegenerative conditions like Alzheimer's, dementia. Stockley (Are Beta blockers safe?, BMJ, 298, 10 Jun 1989) teaches that two patients developed cardiac failure upon administration of nifedipine (a calcium channel blocker, one of the non-beta blockers claimed in claim 24 of the instant application) along with propranolol or atelenol or alprenolol (p 1584, para 2). Hence it is highly unpredictable what the outcome would be due to the interaction of beta blockers with other drugs. Hence there is high unpredictability in the treatment of abnormal autonomic nervous disorders comprising administering a beta blocker with a non-beta blocking agent. Chester et al. (Chest 79, 5, May 1981) teaches adverse effects of propranolol on airway function in nonasthmatic chronic obstructive lung disease patients (see Abstract). The unpredictability of the art is very high because there are large number of diseases associated with aging and a single disease or condition can be diagnosed via multiple biochemical pathways and

treated via multiple biochemical pathways. The scope of enablement varies inversely with the degree of unpredictability of the factors involved, and physiological activity is generally considered to be unpredictable factor. There is a high degree of unpredictability involved in a method of treating a subject for an aging associated condition such as cancer or tumor comprising administering an effective amount of at least one beta-blocker to said subject.

(6, 7) The amount of guidance presented and the presence of working examples:

It has been established that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970). The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. There are no working examples provided in the specification in a method of treating a subject for an aging associated condition such as cancer or tumor comprising providing an effective amount of a beta blocker to a subject to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/ sympathetic activity ratio observed in a healthy 25 year old human subject. The specification does not provide specific examples to provide support to the claims. Also, there is a high degree of unpredictability involved in combining a beta blocker with a

non-beta blocking drug as there may be drug interactions and if there are any adverse effects such combination may not be workable. In summary, Applicant has provided little guidance beyond what was recognized in the art at the time of filing.

(8) The quantity of experimentation needed:

In order to enable the instantly claimed methods commensurate with the entire scope, a large quantity of experimentation would be necessary. Disease states (aging associated conditions) herein claimed do not flow from a single biochemical lesion, but form a range of physiological activities. The instant claimed maladies has no succinct etiological underpinnings, thus the recited conditions are not ameliorated by effecting a single biochemical lesion. That the instant maladies are not attributable to a single etiology, with the basis of the disease stated diffuse and multifaceted, the skilled artisan must treat each compound against the envisioned biochemical lesion to determine the possible use of such compounds in the instant invention. With Applicants' guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct these experiments administering beta blockers for every single aging associated condition and with combination of non-beta blockers (claim 96). Considering the unpredictability of the combination of compounds due to their drug interactions, this would be an arduous and daunting task. It would require undue experimentation to test each beta blocker for all the conditions associated with aging in a method of treating the subjects with aging associated conditions. It would require undue experimentation to test each beta blocker with every single non beta blocking agent for every aging associated condition. It would require undue

experimentation to test all beta blockers for every aging associated condition to produce at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. Though the prior art has taught the use of certain beta blockers in conditions like heart disease, anxiety, hypertension etc. it is not predictable from that data that every beta blocker would be useful in all the aging associated conditions. Aging associated conditions encompasses a large number of conditions including heart diseases, kidney disorder, liver conditions, eye disorders, neurodegenerative disorders, cancers, tumors to name a few. Dosage depends on age, weight, pre-existing conditions, adverse effects, counter indications with drugs taken for other conditions etc. From the state of the prior art and from the guidance provided by the Applicants' it is not predictable that all the aging associated conditions when treated with beta blockers and a non-beta blocking agent would result in producing at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating a subject for an aging associated condition comprising administering an effective amount of at least one beta-blocker and to produce at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion"

and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 85-88, 91-95, 101-104, 107, 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over McBride et al. (Clin Pharmacol Ther July 1988, 93-99) and Autonomic dysfunction document (Review, Duke University, 2000) and Winchell et al. (J of Surgical Research, 63, 11-16, 1996) in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

McBride et al. teaches continuous infusion of propranolol in patients for treating supraventricular tachycardia (aging associated condition, loss of parasympathetic condition as per Applicants' specification, para 201). The reference teaches that all patients had a decrease in heart rate with intravenous propranolol (146+/-24 to 98+/-16 beats/min), Table 3). The reference in p 95, ("propranolol administration") teaches initial maintenance dose and subsequent maintenance doses titrated to individual clinical response.

Autonomic dysfunction document review teaches various methods for assessing autonomic functions including standard cardiovascular autonomic reflex tests, heart rate variability analysis methods etc.

Winchell teaches spectral analysis of heart rate variability (HRV), high frequency (HF, generally represents parasympathetic activity, marker of vagal activity) and low frequency (LF, influenced by both sympathetic and parasympathetic activity). The ratio of HF:LF represents the balance of parasympathetic and sympathetic activity.

It would have been obvious to one having ordinary skill in the art at the time of the invention to have used propranolol a beta-blocker in method of aging associated condition such as tachycardia from the teachings of McBride et al. McBride clearly teaches the use of propranolol in tachycardia patients and also the dosage administration, heart rate changes etc. McBride teaches providing patients associated with supraventricular tachycardia, evaluation of the heart rate (see Table III, before and after treatment). McBride's evaluation of changes in the heart rate in tachycardia patients clearly indicates that modulation of autonomic nervous system is needed. McBride's teachings report administration of an effective amount of beta blocker propranolol in treating an aging associated condition, tachycardia in patients. The HRV (heart rate variability) represents a marker of autonomic activity and has been proposed as a noninvasive index of sympathovagal balance (Task Force of the European Society of Cardiology and North American Society Pacing and Electrophysiology, 1996). The reference does not explicitly teach that administration of beta blockers produce parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's

autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. However, from the prior art teachings it is clear that propranolol modulates the parasympathetic and sympathetic ratio and hence adjusting the dosage ratios accordingly would modulate the system to obtain parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. It is known in the art how to measure parasympathetic activity /sympathetic activity ratio and recruiting healthy adults (25 years old) and measuring the ratio would provide such ratio. A person of ordinary skill in the art from McBride's, Winchell and Autonomic dysfunction document would have found it obvious to adjust the dosage of the same beta blocker (propranolol) claimed to obtain the parasympathetic activity /sympathetic activity ratio analogous to that a 25 year old human subject as it is well within the skill of an ordinary artisan. One having ordinary skilled in the art at the time of the invention would have been motivated to determine the parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system is to use the ratio as an indicator and would have used propranolol to obtain the therapeutic benefits in tachycardia patients.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize.

Claim 109 is rejected under 35 U.S.C. 103(a) as being unpatentable over McBride et al. (Clin Pharmacol Ther July 1988, 93-99) and Autonomic dysfunction document (Review, Duke University, 2000) and Winchell et al. (J of Surgical Research, 63, 11-16, 1996) in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003) as applied to claims 85-88, 91-95, 101-104, 107, 108 above and further in view of Mehmanesh et al. (The Annals of Thoracic Surgery, 1998, 65, 632-636).

McBride et al., Autonomic dysfunction document, Winchell et al. and Mann's teachings discussed as above.

The references do not teach the use of electrode in treating an aging associated condition like tachycardia.

Mehmanesh teaches atrial electrode for the treatment of supraventricular tachycardia (see abstract).

A person of ordinary skill in the art at the time of the invention would have found it obvious to use an electrode to treat supraventricular tachycardia in patients from the teachings of Mehmanesh et al. A person of ordinary skill in the art would have been motivated to use an electrode to treat supraventricular tachycardia in expectation of therapeutic benefits and in using in combination with a beta blocker to obtain synergistic or additive effects in treating tachycardia.

Claims 96-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over McBride et al. (Clin Pharmacol Ther July 1988, 93-99) and Autonomic dysfunction document (Review, Duke University, 2000) and Winchell et al. (J of Surgical Research, 63, 11-16, 1996) in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003) as applied to claims 85-88, 91-95, 101-104, 107, 108 above and further in view of Gaida et al. (US 20030171391).

McBride et al., Autonomic dysfunction document, Winchell et al. and Mann's teachings discussed as above.

The references do not teach the use of a non-beta blocker such as NSAID in treating an aging associated condition like tachycardia.

Gaida teaches treating diseases including cardiac arrhythmia comprising administering ambroxol and non-steroidal analgesics (see claims 1, 5 and 7).

Furthermore the reference teaches ibuprofen as one of the pain relieving non-steroidal analgesic agent (see para 0016, 17).

A person of ordinary skill in the art at the time of the invention would have found it obvious to use NSAID, such as ibuprofen to treat tachycardia or arrhythmia in patients from the teachings of Gaida et al. A person of ordinary skill in the art would have been motivated to use an NSAID, such as ibuprofen to treat tachycardia or arrhythmia in expectation of therapeutic benefits (pain reliever) and in using in combination with a beta blocker to obtain synergistic or additive effects in treating tachycardia.

Claims 85-88, 91-95, 100-104, 107-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al. (J clin Invest 1990, 85, 836-842) and Autonomic dysfunction document (Review, Duke University, 2000) and Winchell et al. (J of Surgical Research, 63, 11-16, 1996) in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Murray et al. teaches oral administration of propranolol (40 mg) orally every 6 h and dosage increased every 2d until arrhythmia (tachycardia) suppression. Effective dosages ranged from 320-1280 mg/d and arrhythmia suppression occurred in six patients (see Abstract). In table II, the reference reports the exercise testing during d and dl propranolol therapy. In the Methods section the reference teaches subsequent administration of propranolol. The reference in Results section (para 1) teaches that 10 male patients ages 35-71 participated in the arrhythmia suppression trial (see also Methods). Thus providing subjects with an aging associated condition is taught by

Murray et al. In summary, Murray's teachings indicate that propranolol is useful in treating arrhythmia or tachycardia in patients.

Autonomic dysfunction document and Winchell et al. teachings discussed as above.

It would have been obvious to one having ordinary skill in the art at the time of the invention to have used propranolol a beta-blocker in method of aging associated condition such as arrhythmia or tachycardia from the teachings of Murray et al. Murray et al. clearly teaches the use of propranolol in tachycardia patients and also the dosage administration, heart rate changes etc. Murray et al. evaluation of changes in the heart rate in tachycardia patients clearly indicates that modulation of autonomic nervous system is needed. Murray et al. teachings report administration of an effective amount of beta blocker propranolol in treating an aging associated condition, tachycardia in patients. Murray et al. teaches effective dosages ranged from 320-1280 mg/d and subsequent administration (meets the limitation of at least 24 hours, claim 101). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence administration of the same compound with the suggested dosage amount (as in the specification of the instant application) to a subject with an autonomic nervous system abnormality condition would produce the same pharmacological effects of producing parasympathetic activity/sympathetic activity ratio in at least a portion of said subject’s autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. In addition,

the prior art teachings it is clear that propranolol modulates the parasympathetic and sympathetic ratio and hence adjusting the dosage ratios accordingly would modulate the system to obtain parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. The HRV (heart rate variability) represents a marker of autonomic activity and has been proposed as a noninvasive index of sympathovagal balance (Task Force of the European Society of Cardiology and North American Society Pacing and Electrophysiology, 1996). It is known in the art how to measure parasympathetic activity /sympathetic activity ratio and recruiting healthy adults (25 years old) and measuring the ratio would provide such ratio. A person of ordinary skill in the art from Murray's, Winchell and Autonomic dysfunction document would have found it obvious to adjust the dosage of the same beta blocker (propranolol) claimed to obtain the parasympathetic activity /sympathetic activity ratio analogous to that a 25 year old human subject as it is well within the skill of an ordinary artisan. One having ordinary skilled in the art at the time of the invention would have been motivated to determine the parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system is to use the ratio as an indicator and would have used propranolol to obtain the therapeutic benefits in tachycardia patients.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize.

Claim 109 is rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al. (J clin Invest 1990, 85, 836-842) and Autonomic dysfunction document (Review, Duke University, 2000) and Winchell et al. (J of Surgical Research, 63, 11-16, 1996) in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003) as applied to claims 85-88, 91-95, 100-104, 107-108 above and further in view of Mehmanesh et al. (The Annals of Thoracic Surgery, 1998, 65, 632-636).

Murray et al., Autonomic dysfunction document, Winchell et al. and Mann's teachings discussed as above.

The references do not teach the use of electrode in treating an aging associated condition like tachycardia.

Mehmanesh teaches atrial electrode for the treatment of supraventricular tachycardia (see abstract).

A person of ordinary skill in the art at the time of the invention would have found it obvious to use an electrode to treat supraventricular tachycardia in patients from the teachings of Mehmanesh et al. A person of ordinary skill in the art would have been motivated to use an electrode to treat supraventricular tachycardia in expectation of therapeutic benefits and in using in combination with a beta blocker to obtain synergistic or additive effects in treating tachycardia.

Claims 96-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al. (J clin Invest 1990, 85, 836-842) and Autonomic dysfunction document (Review, Duke University, 2000) and Winchell et al. (J of Surgical Research, 63, 11-16, 1996) in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003) as applied to claims 85-88, 91-95, 100-104, 107-108 above and further in view of Gaida et al. (US 20030171391).

Murray et al., Autonomic dysfunction document, Winchell et al. and Mann's teachings discussed as above.

The references do not teach the use of a non-beta blocker such as NSAID in treating an aging associated condition like tachycardia.

Gaida teaches treating diseases including cardiac arrhythmia comprising administering ambroxol and non-steroidal analgesics (see claims 1, 5 and 7).

Furthermore the reference teaches ibuprofen as one of the pain relieving non-steroidal analgesic agent (see para 0016, 17).

A person of ordinary skill in the art at the time of the invention would have found it obvious to use NSAID, such as ibuprofen to treat tachycardia or arrhythmia in patients from the teachings of Gaida et al. A person of ordinary skill in the art would have been motivated to use an NSAID, such as ibuprofen to treat tachycardia or arrhythmia in expectation of therapeutic benefits (pain reliever) and in using in combination with a beta blocker to obtain synergistic or additive effects in treating tachycardia.

Claims 85-88, 91-93, 95, 100-104, 107-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mueller et al. (Clin Cardiol. 2, 393-403, 1979) and Autonomic dysfunction document (Review, Duke University, 2000) and Winchell et al. (J of Surgical Research, 63, 11-16, 1996) in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Mueller et al. teaches administration of propranolol (0.1 mg/kg) to 55 patients with myocardial infarction. The reference further teaches continuous treatment with oral administration of propranolol 56+/-20 mg q6h for 10 days (see summary, Materials and Methods, Experimental Procedure). The reference teaches in p 394, col. 1, para 2, that propranolol administration reduces oxygen requirements by decreasing heart rate and myocardial contractility. Fig. 3 and Fig. 4, depicts the effects of propranolol on heart rate, arterial pressure and pulmonary wedge pressure, cardiac index, pulmonary artery oxygen tension, systemic vascular resistance and left ventricular ejection fraction.

Autonomic dysfunction document and Winchell et al. teachings discussed as above.

It would have been obvious to one having ordinary skill in the art at the time of the invention to have used propranolol a beta-blocker in method of aging associated condition such as myocardial infarction from the teachings of Mueller et al. Mueller et al. clearly teaches the use of propranolol in myocardial infarction patients and also the dosage administration, heart rate changes etc. Mueller et al.'s evaluation of changes in the heart rate in tachycardia patients clearly indicates that modulation of autonomic nervous system is needed. Mueller et al. teachings report administration of an effective amount of beta blocker propranolol in treating an aging associated condition, myocardial infarction in patients. Mueller et al. teaches effective dosages of 56+/-20 mg q6h and subsequent administration (meets the limitation of at least 24 hours, claim 101). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence administration of the same compound with the suggested dosage amount (as in the specification of the instant application) to a subject with an autonomic nervous system abnormality condition would produce the same pharmacological effects of producing parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. In addition, the prior art teachings it is clear that propranolol modulates the parasympathetic and sympathetic ratio and hence adjusting the dosage ratios accordingly would modulate

the system to obtain parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. It is known in the art how to measure parasympathetic activity /sympathetic activity ratio and recruiting healthy adults (25 years old) and measuring the ratio would provide such ratio. The HRV (heart rate variability) represents a marker of autonomic activity and has been proposed as a noninvasive index of sympathovagal balance (Task Force of the European Society of Cardiology and North American Society Pacing and Electrophysiology, 1996). A person of ordinary skill in the art from Mueller et al.'s, Winchell and Autonomic dysfunction document would have found it obvious to adjust the dosage of the same beta blocker (propranolol) claimed to obtain the parasympathetic activity /sympathetic activity ratio analogous to that a 25 year old human subject as it is well within the skill of an ordinary artisan. One having ordinary skilled in the art at the time of the invention would have been motivated to determine the parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system is to use the ratio as an indicator and would have used propranolol to obtain the therapeutic benefits in tachycardia patients.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize.

Claim 109 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mueller et al. (Clin Cardiol. 2, 393-403, 1979) and Autonomic dysfunction document (Review, Duke University, 2000) and Winchell et al. (J of Surgical Research, 63, 11-16, 1996) in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003) as applied to claims 85-88, 91-93, 95, 100-104, 107-108 above and further in view of Mehmanesh et al. (The Annals of Thoracic Surgery, 1998, 65, 632-636).

Mueller et al., Autonomic dysfunction document, Winchell et al. and Mann's teachings discussed as above.

The references do not teach the use of electrode in treating an aging associated condition like tachycardia.

Mehmanesh teaches atrial electrode for the treatment of supraventricular tachycardia (see abstract).

A person of ordinary skill in the art at the time of the invention would have found it obvious to use an electrode to treat supraventricular tachycardia in patients from the teachings of Mehmanesh et al. A person of ordinary skill in the art would have been motivated to use an electrode to treat supraventricular tachycardia in expectation of therapeutic benefits and in using in combination with a beta blocker to obtain synergistic or additive effects in treating tachycardia.

Claims 96-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mueller et al. (Clin Cardiol. 2, 393-403, 1979) and Autonomic dysfunction document (Review, Duke University, 2000) and Winchell et al. (J of Surgical Research, 63, 11-16, 1996) in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003) as applied to claims 85-88, 91-93, 95, 100-104, 107-108 above and further in view of Gottlieb et al. (US 20050215533, effective filing date Jul 9 2002).

Mueller et al., Autonomic dysfunction document, Winchell et al. and Mann's teachings discussed as above.

The references do not teach the use of a non-beta blocker such as NSAID in treating an aging associated condition like tachycardia.

Gottlieb et al. teaches treating reperfusion injury associated with myocardial infarction comprising administering serotonin reuptake inhibitor, antidepressant etc. with

a non-steroidal anti-inflammatory drug (see claim 11). In para 0074 the reference teaches ibuprofen as one of the NSAID's as a substrate of 2C9 enzyme.

A person of ordinary skill in the art at the time of the invention would have found it obvious to use NSAID, such as ibuprofen to treat myocardial infarction in patients from the teachings of Gottlieb et al. A person of ordinary skill in the art would have been motivated to use an NSAID, such as ibuprofen to treat myocardial infarction in expectation of therapeutic benefits (to inhibit reperfusion injury associated with myocardial infarction) and in using in combination with a beta blocker to obtain synergistic or additive effects in treating myocardial infarction.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 85-88, 91-98, 107, 108 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1, 9, 22 and 24 of co-pending application No. 10/962,190 in view of Davies et al. (The J of Intl Med Research, 1988, 16, 173-181).

The rejected claims are directed to a directed to a method comprising providing a subject known to suffer from an aging associated condition; determining the state of the autonomic nervous system by measuring a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system; evaluating the parasympathetic activity/sympathetic activity ratio to determine if modulation of the autonomic nervous system is needed; and administering to said subject an effective amount of at least one beta- blocker if modulation of the autonomic nervous system is needed to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/ sympathetic activity ratio observed in a healthy 25 year old human subject to treat said subject for said aging associated condition. The claims include administration of a second non-beta blocker, NSAID.

Claims 1, 9, 22 and 24 of the co-pending application ‘190 teach a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject’s autonomic nervous system comprising administering at least one aldosterone antagonist or an analogue thereof such as a beta blocker to treat at least one conditions such as; neurodegenerative

conditions; gastrointestinal conditions; genitourinary conditions; aging associated conditions etc.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the co-pending application teaches a method of treating autonomic nervous system abnormality comprising administering an agent such as a beta blocker in modulating at least a portion of parasympathetic/sympathetic activity.

The co-pending application does not teach administration of a non-beta blocking agent such as NSAID in a method of treating an autonomic nervous condition such as aging associated condition including hypertension.

Davies et al. teach the administration of ibuprofen, a non-steroidal anti-inflammatory drug along with an anti-hypertensive agent and a beta-blocker such as propranolol (see Abstract) to group of patients with hypertension.

It would have been obvious to one having ordinary skill in the art at the time of the invention to have added an NSAID along with a beta blocker such as propranolol in treating hypertension, an aging associated condition from the teachings of Davies et al. because the reference teaches that ibuprofen may be routinely administered to patients receiving propranolol without loss of control of the anti-hypertensive action of the drug.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 85-88, 91-98, 107, 108 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 117-120, 131-132 of co-pending application No. 10/962,190 in view of Davies et al. (The J of Intl Med Research, 1988, 16, 173-181).

The rejected claims are directed to a directed to a method comprising providing a subject known to suffer from an aging associated condition; determining the state of the autonomic nervous system by measuring a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system; evaluating the parasympathetic activity/sympathetic activity ratio to determine if modulation of the autonomic nervous system is needed; and administering to said subject an effective amount of at least one beta- blocker if modulation of the autonomic nervous system is needed to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/ sympathetic activity ratio observed in a healthy 25 year old human subject to treat said subject for said aging associated condition. The claims include administration of a second non-beta blocker, NSAID.

Claims 117-120, 131-132 of co-pending application ‘190 is towards a method of modulating at least a portion of a subject’s autonomic condition to treat aging associated conditions.

The co-pending application does not teach the use of a beta blocker in treating an aging associated condition.

Davies et al. teach the administration of ibuprofen, a non-steroidal anti-inflammatory drug along with an anti-hypertensive agent and a beta-blocker such as propranolol (see Abstract) to group of patients with hypertension.

It would have been obvious to one having ordinary skill in the art at the time of the invention to have used added a beta blocker (e.g. propranolol) and an NSAID along in treating hypertension, an aging associated condition from the teachings of Davies et al. because the reference teaches the use of propranolol and ibuprofen in hypertensive patients.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 85-88, 91-95, 107-109 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 27 and 30 of U.S. Patent 7,149,574.

The rejected claims are directed to a directed to a method comprising providing a subject known to suffer from an aging associated condition; determining the state of the autonomic nervous system by measuring a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system; evaluating the parasympathetic activity/sympathetic activity ratio to determine if modulation of the autonomic nervous system is needed; and administering to said subject an effective amount of at least one beta- blocker if modulation of the autonomic nervous system is needed to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the

parasympathetic activity/ sympathetic activity ratio observed in a healthy 25 year old human subject to treat said subject for said aging associated condition.

Claims 1, 27 and 30 of the patent is towards a method of modulating at least a portion of a subject's autonomic condition to treat neurodegenerative diseases, gastrointestinal disorders, genitourinary disorders etc. (aging associated conditions) comprising electrically modulating at least a portion of said subject's autonomic nervous system (ANS) with additional pharmacological agent, beta blocker (claim 30).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the patent teaches a method of modulating ANS comprising administering a beta blocker and electrical stimulation in treating aging associated conditions such as neurodegenerative conditions.

Claims 85-88, 91-95, 107-109 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 27 and 30 of U.S. Patent 7,363,076.

The rejected claims are directed to a directed to a method comprising providing a subject known to suffer from an aging associated condition; determining the state of the autonomic nervous system by measuring a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system; evaluating the parasympathetic activity/sympathetic activity ratio to determine if modulation of the autonomic nervous system is needed; and administering to said subject an effective amount of at least one beta- blocker if modulation of the autonomic nervous system is needed to produce a parasympathetic activity/sympathetic activity ratio in at least a

portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/ sympathetic activity ratio observed in a healthy 25 year old human subject to treat said subject for said aging associated condition.

Claims 1, 10, 48, 59 of the patent is towards a method of modulating at least a portion of a subject's autonomic condition to treat neurodegenerative diseases, cardiovascular conditions, cancer, gastrointestinal disorders, genitourinary disorders etc. (aging associated conditions, claims 48) comprising electrically modulating at least a portion of said subject's autonomic nervous system (ANS) with additional pharmacological agent, beta blocker (claim 10, 59).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the patent teaches a method of modulating ANS comprising administering a beta blocker in treating aging associated conditions such as neurodegenerative conditions, cancer etc.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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